

## Editorial

## Do prenatal risk factors cause psychiatric disorder? Be wary of causal claims

Anita Thapar and Michael Rutter

**Summary**

Many prenatal risk factors are known to have adverse consequences on fetal development and there is increasing interest in effects on the mental health of offspring.

However, associations with prenatal risk factors may arise because of postnatal risk or through confounders, including

inherited ones. As a result, caution is required in assuming causation.

**Declaration of interest**

None.

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### Impact of prenatal risk factors on fetal development

The consequences of prenatal hazards on the fetus are well known. For example, the teratogenic effects of thalidomide, rubella and high levels of alcohol exposure in early pregnancy are undisputed and have been appreciated for many years, as they result in identifiable congenital defects. It has gradually come to be realised however that exposure to adversity later in pregnancy could involve a broader set of risks on fetal development that are less immediately obvious in that they do not result in identifiable stigmata.<sup>1</sup>

One example is exposure to maternal smoking in pregnancy. It is well established that exposure to cigarette smoke *in utero* results in lower offspring birth weight and this is generally considered to arise because of the effects of specific toxins on late fetal development. Other prenatal adversities such as poor fetal nutrition are thought to affect development in a different fashion; specifically by some form of biological programming.<sup>1</sup> Here, exposure to early adversity during a sensitive period of development is thought to lead to structural, physiological and metabolic changes in the fetus that do not cause recognisable defects but increase susceptibility to later disease. The link between lower birth weight, an index of fetal nutrition, and increased rates of adult cardiovascular diseases is assumed to arise from this type of programming effect.

### Evidence that prenatal risk factors are linked to subsequent mental health

These findings have been accompanied by a rapidly expanding research literature claiming that prenatal factors have long-lasting consequences on later mental health.<sup>1</sup> One of the most robust findings relates to exposure to maternal smoking in pregnancy, which has been repeatedly observed to be associated with offspring attention-deficit hyperactivity disorder (ADHD) and antisocial behaviour.<sup>2</sup> There have also been many studies showing links between lower birth weight<sup>3</sup> and a wide range of psychopathology, including depression, schizophrenia and ADHD, implying that

undernutrition in pregnancy may affect risk for later psychiatric disorder. Another important example is exposure to gestational stress,<sup>3</sup> which has been related to increased rates of offspring psychopathology, notably anxiety, depression and ADHD.

Several plausible but speculative mechanisms could account for these links between prenatal risk factors and mental health outcomes. These include fetal damage from disruption to placental function, exposure to anoxia, maternal cortisol, environmental toxins such as nicotine and carbon monoxide that cross the placental barrier, and early programming effects. Epigenetic changes (non-inherited changes to the genome) might mediate programming effects at a molecular level,<sup>1</sup> although that is not yet proven.

### Associated prenatal risk factors are not necessarily causal

A powerful means of testing causal effects is through experimental methods.<sup>4</sup> However, randomised controlled trials involving exposure to the prenatal environment are almost always unethical or not feasible. Natural experiments, where total populations have 'accidentally' been exposed to the prenatal risk factor, can be useful.<sup>4</sup> For example, the Dutch<sup>5</sup> and Chinese<sup>6</sup> famine studies suggested increased rates of schizophrenia in offspring exposed to famine-induced undernutrition *in utero*. However, most studies rely on data involving the possibility of selection where exposure to the prenatal risk factor is not random.

There are two main reasons why it is likely that some of the numerous observations of statistical associations between prenatal risks (such as maternal smoking and stress) and mental health outcomes may not reflect causation. First, many of the putative prenatal risks such as maternal smoking and stress in pregnancy are ones that tend to be associated with postnatal risks (e.g. parent mental health problems, social adversity) for offspring psychiatric disorder. Accordingly, it is crucial to use designs that can separate prenatal from postnatal effects.<sup>1</sup> Second, there may be unmeasured confounders, including maternally transmitted inherited factors. As many prenatal risks derive from heritable maternal behaviours (e.g. smoking), and because mothers transmit genes to their offspring, there is the possibility that the associations arise through mothers and offspring sharing some of their genome rather than because of a true prenatal risk effect. Thus, there is also a need to be able to test the effects of prenatal risk independent of the relationship between maternal and offspring genomes using genetically sensitive designs.<sup>7</sup>

Traditionally, epidemiological designs have tended to deal with these two possibilities by adjusting for measured confounders such

as social class and parent psychopathology. This type of statistical approach is of course appropriate. However, as highlighted by many,<sup>7</sup> it is problematic because it relies on adequate measurement of the confounding variable and does not deal with unrecognised, unmeasured 'residual' confounding not tapped by the available measures.<sup>7</sup>

Are these relevant problems with regard to the links between prenatal risk factors and psychopathology? We believe they are. First, considering the separation of pre- and postnatal effects, a good example is provided by findings from animal studies that show that many of the effects of prenatal stress on offspring behaviour in animals are mediated by the postnatal rearing environment and ameliorated by postnatal environmental enrichment. Human studies suggest similar findings in that concurrent maternal stress and mental health appear to be influential. However, some of these studies imply that it is the prenatal risk effects that are important even though this is not a safe or correct assumption. Second, residual confounding is a problem, as shown by findings from genetically sensitive designs. We use as the example exposure to maternal smoking in pregnancy and offspring ADHD.

### A cautionary tale: maternal smoking in pregnancy and offspring ADHD

One of the most widely replicated findings in this area of research is the link between exposure to maternal smoking in pregnancy and increased risk of ADHD in offspring. Here, the observational evidence for association is very convincing by most standards. Numerous case-control and cohort studies, including a pooled analysis, demonstrate association even when confounders including postnatal environmental factors such as parent psychopathology are included.<sup>2</sup> Moreover there is evidence of a dose-response relationship between the number of cigarettes smoked and ADHD severity in some studies. Finally, smoking in pregnancy is known to result in lower birth weight and similar mechanisms such as exposure to carbon monoxide or altered placental function could account for risk effects on ADHD.

However, could the association reflect inheritance, as both maternal smoking and ADHD are genetically influenced? Maternal smoking in pregnancy also indexes familial risks associated with psychopathology. Thus we cannot assume a causal effect of maternal smoking in pregnancy and ADHD.

Recent evidence suggests such caution is warranted. There are two designs where it has been possible to remove the problem of maternal and offspring genome sharing being paired with exposure to maternal smoking. Studies of the children of twins<sup>8</sup> and also children who are genetically unrelated to the woman undergoing the pregnancy as a result of conception through assisted reproductive technologies allow separation of prenatal effects from maternal-child genome sharing.<sup>9</sup> Both types of design have suggested that the link between exposure to maternal smoking in pregnancy and lower offspring birth weight is a confirmed prenatal effect.<sup>1</sup> In contrast, for ADHD and antisocial behaviour<sup>9</sup> the association may be explained by inherited factors transmitted from mother to child. Similar results have come from sibling studies, where one sibling is exposed to maternal smoking in pregnancy and the other is not, but the unexposed sibling also shows increased attentional and behavioural problems.<sup>10</sup> Finally, animal study findings have been inconclusive. Whereas animal studies consistently show that exposure to cigarette smoke and nicotine *in utero* reduces birth weight, for ADHD-like behaviours the evidence is mixed. When taken together, all these findings across different designs suggest that the claim that maternal

smoking in pregnancy causes ADHD in offspring may be unfounded or the effects may be much smaller than currently believed. The results highlight that inferring causal effects of prenatal risk factors from epidemiological studies alone, even when potential confounders are included, can be problematic.

### Implications for the clinician

We highlight that despite current popular belief that prenatal risk factors are important for psychopathology, there are perils in assuming that control for known confounders necessarily allows inference of causal influences. Currently the majority of evidence on the links between prenatal risk factors and mental health comes from epidemiological/observational studies. We emphasise the need for different types of designs to exclude causality or test for consistency with a causal hypothesis. Reducing the risk of a specific outcome will only be effective if there is a true causal relationship with the prenatal factor and thus such research needs to be undertaken. If it is the postnatal rather than the prenatal period that is important for psychopathology, there are important policy and practice implications as to when to intervene and what to target. If associations are spurious because of inherited confounders, then it is essential for families, clinicians or researchers to be wary of causal claims.

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